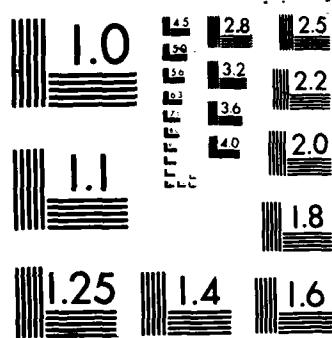


AD-A175 429 STABILIZATION OF CENTRAL BIOSYNTHETIC ENZYME DYNAMICS 1/1
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JOLLA DEPT OF PSYCHIATRY A J MANDELL 01 OCT 86
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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) We have developed a battery of quantifiers with which to examine time series in biological observables. Our fundamental finding is that loss of entropy spells dysfunction in signal-sensitive biological dynamics. In the case of rate-limiting enzymes in the synthesis of biogenic amine transmitters, treatments and conditions that retarded emergent periodicity in the time-dependent or substrate/ligand dependent dynamics tended to prevent the desensitized state.		

Final Report for DAAG29-83-K-0069

Stabilization of Central Biosynthetic Enzyme Dynamics
Against Cholinergic PerturbationArnold J. Mandell, M.D.
University of California, San Diego

Stabilization have been developed

The major focus of our work has been the development of measure theoretic techniques for the evaluation of enzyme kinetic stability. Motivated by the phenomena of reversible and irreversible "aging" in cholinergic peripheral and central neural enzymes following neurotoxic exposure and the toxic effects of conventional antagonists, we tried to establish the basis for an alternative strategy: the delay of irreversibility through understanding the dynamics of phase transitions in brain enzymes.

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Our fundamental finding was the counterintuitive evidence that loss of complexity and emergent coherence in the kinetic dynamics of brain enzymes signaled their impending desensitization. Treatments and conditions that retarded emergent periodicity or even smoothness in the time-dependent or substrate-ligand dependent dynamics of these proteins tended to prevent the desensitized state. We called such substances "mixing" and suggested very low levels of lithium, far below prevailing clinical doses, as one such mixing agent. It prevented emergent pathological order in the kinetics of the brain enzymes in our studies.

The technical accomplishments of our work centered around the development of a battery of fourteen quantifiers of complexity useful in examining time series of biological observables (from enzyme activity to rat exploratory behavior) which has been and is being used in a variety of biological contexts. In contrast to the thermodynamic systems of physics, in signal-sensitive biological dynamics entropy loss (not gain) spells dysfunction. As with Shannon's channel, complexity greater than that of the sender is required for receipt and decoding of information by a receiver. Our measures are extremely sensitive to small changes in entropy and are currently being used

to predict sudden cardiac arrest in circumstances when the heart (due to coherent order) no longer "listens."

Patrick Russo earned a Ph.D. in Neurosciences while participating in the research supported by this contract. His dissertation is titled: The Characterization of Rat Brain Tyrosine Hydroxylase and Rat Locomotor Behavior: The Application of Nonlinear Dynamic Concepts, and a copy is incorporated with this report.

In addition to publications submitted with earlier progress reports, work detailed in four additional publications was supported all or in part by this contract. Memoranda of transmittal are attached to the requisite copies of these new publications:

1. Mandell, Arnold J.: Prime times: the distribution of singularities in hydrophobic free energy of proteins. In: M.F. Shlesinger, R. Cawley, A.W. Saenz, and W. Zachary, Perspectives in Nonlinear Dynamics, World Scientific, 1986, pp. 259-277.
2. Mandell, Arnold J.: The hyperbolic helix hypothesis: Stapleton's fractal measure on the hydrophobic free energy mode distributions of allosteric proteins. In: L. Pietronero and E. Tosatti, eds.: Fractals in Physics, Elsevier Science Publishers, 1986, pp. 469-474.
3. Mandell, Arnold J: Desensitization, emergent differentiability, and loss of fractal scaling in the power spectra of brain proteins. In: Fractal Aspects of Materials, Materials Research Society, Boston, 1985
4. Mandell, Arnold J., Russo, Patrick V., and Blomgren, Barbara W., Geometric universality in brain allosteric protein dynamics; complex hydrophobic transformation predicts mutual recognition by polypeptides and proteins. Ann. New York Acad. Sci. 1986, in press.



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